



## General

### Guideline Title

Recommendations on disease management for patients with advanced human epidermal growth factor receptor 2-positive breast cancer and brain metastases: American Society of Clinical Oncology clinical practice guideline.

### Bibliographic Source(s)

Ramakrishna N, Temin S, Chandarlapaty S, Crews JR, Davidson NE, Esteva FJ, Giordano SH, Gonzalez-Angulo AM, Kirshner JJ, Krop I, Levinson J, Modi S, Patt DA, Perez EA, Perlmutter J, Winer EP, Lin NU. Recommendations on disease management for patients with advanced human epidermal growth factor receptor 2-positive breast cancer and brain metastases: American Society of Clinical Oncology clinical practice guideline. *J Clin Oncol*. 2014 Jul 1;32(19):2100-8. [56 references] [PubMed](#)

### Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

## Recommendations

### Major Recommendations

Definitions for the rating of evidence (High, Intermediate, Low, Insufficient); types of recommendations (Evidence-based, Formal Consensus, Informal Consensus, No Recommendation); and strength of recommendations (Strong, Moderate, Weak) are provided at the end of the "Major Recommendations" field.

Note: Recommendation strength is weak for all recommendations, unless otherwise stated.

#### Clinical Question

What is the appropriate course of treatment for patients with human epidermal growth factor receptor 2 (HER2)-positive advanced breast cancer and brain metastases?

#### Clinical Question A

Does the approach to local therapy of brain metastases differ in patients with HER2-positive breast cancer?

#### *Recommendation 1 (single brain metastasis, favorable prognosis)*

If a patient has a favorable prognosis for survival and a single brain metastasis, he or she should be evaluated by an experienced neurosurgeon for

discussion of the option of surgical resection, particularly if the metastasis is  $>3$  to 4 cm and/or if there is evidence of symptomatic mass effect. Evidence quality: intermediate. Recommendation strength: strong.

IA. If a patient has a favorable prognosis and a single brain metastasis  $<3$  to 4 cm without symptomatic mass effect, clinicians may offer either stereotactic radiosurgery (SRS) or surgical resection, depending on the location and surgical accessibility of the tumor, need for tissue diagnosis, and other considerations, such as medical risk factors for surgery and patient preference. Evidence quality: intermediate.

If these patients choose to undergo SRS, clinicians may discuss the options of adding whole brain radiotherapy (WBRT) to SRS versus SRS alone. Evidence quality: intermediate.

IB. For most patients with brain metastases who undergo surgical resection, clinicians should recommend postoperative radiotherapy to the resection bed to reduce the risk of local recurrence. Evidence quality: intermediate.

IC. If a patient has a favorable prognosis and a single brain metastasis  $>3$  to 4 cm, which is deemed unresectable and unsuitable for SRS, clinicians may discuss the options of WBRT or fractionated stereotactic radiotherapy. Evidence quality: low.

ID. After treatment, serial imaging every 2 to 4 months may be used to monitor for local and distant brain failure. Evidence quality: low.

Note that there is more high-level evidence to support WBRT compared with SRS to the resection cavity. However, routine postoperative WBRT does not seem to confer a survival benefit. Recommendation IIIB provides a definition of favorable prognosis.

#### *Recommendation II (limited metastases [two to four metastases] and favorable prognosis)*

If a patient has a favorable prognosis and presents with multiple, but limited, metastases (two to four), treatment options depend on the size, resectability, and mass effect of the lesions.

IIA. In a patient who presents with limited metastases suitable for SRS, clinicians may discuss SRS with or without WBRT. Evidence quality: intermediate.

IIB. In a patient who has a large ( $>3$  to 4 cm) lesion associated with symptomatic mass effect, clinicians may discuss surgical resection of the larger lesion, if the lesion is deemed resectable. The remaining lesions may be treated with SRS with or without WBRT. Evidence quality: intermediate.

IIC. In a patient with lesions that are unresectable and unsuitable for SRS, clinicians may recommend WBRT and may discuss SRS after WBRT. Evidence quality: low.

Note that special circumstances include favorable prognosis and favorable risk-benefit ratio (i.e., cases of symptomatic mass effect). Unsuitable refers to metastases  $>3$  to 4 cm or if SRS would result in excess dose to critical radiosensitive brain structures, such as the brainstem or optic nerves/chiasm. The addition of WBRT to SRS in patients with one to four brain metastases is associated with decreased local and distant brain failure, but no survival benefit.

#### *Recommendation III (diffuse disease/extensive metastases)*

IIIA. If a patient has symptomatic leptomeningeal metastases (specifically in the brain), clinicians may recommend WBRT. The management of leptomeningeal metastases is complex, and recommendations regarding intrathecal therapy or systemic therapy for leptomeningeal metastases are outside the scope of this practice guideline. Evidence quality: low. Recommendation strength: moderate.

IIIB. If a patient has a more favorable prognosis and presents with many diffuse/brain metastases ( $\geq$  five metastases), clinicians may recommend WBRT. Patients with favorable prognoses are those with good performance status and effective systemic therapy options. The criteria may include Karnofsky Performance Status (KPS)  $\geq 70$ , age, controlled extracranial disease, and/or whether good salvage systemic therapy options for extracranial disease are available. Evidence quality: low.

#### *Recommendation IV (patients with poor prognosis)*

If a patient has brain metastases and a poor prognosis, clinicians should discuss the options of best supportive care and/or palliative care, which may or may not include radiation therapy, on a case-by-case basis. Evidence quality: low.

IVA. For a patient with symptomatic brain metastases and poor prognosis, WBRT may be offered if there is a reasonable expectation of symptomatic improvement that outweighs the acute and subacute treatment-related toxicities, including fatigue and decline in neurocognitive function. Evidence quality: low.

#### *Recommendation V (patients with progressive intracranial metastases despite initial therapy)*

If a patient has progressive intracranial metastases, treatment options will depend on the patient's prior therapies, burden of disease, performance status, and overall prognosis.

VAI (brain recurrence and irradiation; limited recurrence). For a patient with a favorable prognosis and limited recurrence after treatment with WBRT, clinicians may discuss SRS, surgery, a trial of systemic therapy, or enrollment onto a clinical trial. For a patient with a favorable prognosis and limited recurrence after treatment with SRS, clinicians may discuss repeat SRS, surgery, WBRT, a trial of systemic therapy, or enrollment onto a clinical trial. Evidence quality: low. Recommendation strength: moderate.

VAIIa (diffuse recurrence). If a patient has diffuse recurrence after treatment with WBRT, clinicians may discuss palliative options such as repeat reduced dose WBRT, a trial of systemic therapy, enrollment onto a clinical trial, or best supportive care. Evidence quality: low.

VAIIb (diffuse recurrence). If a patient has diffuse recurrence after treatment with SRS, clinicians may discuss palliative options such as WBRT, a trial of systemic therapy, enrollment onto a clinical trial, or best supportive care. Evidence quality: low. Recommendation strength: moderate.

#### Clinical Question B

How should systemic therapy be managed in patients with HER2-positive brain metastases (including management of systemic therapy when the brain is the only site of progression versus when progression occurs in both brain and elsewhere)?

#### *Recommendation VB (brain recurrence and systemic therapy)*

VBI. For a patient who receives a standard surgical- or radiotherapy-based approach to treat brain metastases and is receiving anti-HER2-based therapy and whose systemic disease is not progressive at the time of brain metastasis diagnosis, clinicians should not switch systemic therapy. Evidence quality: low. Recommendation strength: moderate.

VBII. For a patient who receives a standard surgical- and/or radiotherapy-based approach to treatment of brain metastases and whose systemic disease is progressive at the time of brain metastasis diagnosis, clinicians should offer HER2-targeted therapy according to the algorithms for treatment of HER2-positive metastatic breast cancer. (For example, a patient who has been maintained on single-agent trastuzumab and develops isolated progression in the brain should have his or her brain metastases treated and trastuzumab continued.) Evidence quality: intermediate. Recommendation strength: moderate.

#### Clinical Question C

Is there a role for systemic therapy specifically to treat brain metastases in HER2-positive breast cancer?

#### *Recommendation VI (systemic treatment for brain metastases)*

VIA. If a patient has asymptomatic, low-volume brain metastases and has not received radiation therapy, clinicians may discuss upfront therapy with lapatinib and capecitabine as an option. Clinicians should discuss the most recent data and inform patients that radiation therapy in this setting is still the primary option. Evidence quality: low.

VIB. If a patient develops intracranial disease progression after WBRT or SRS (including when patient is not a candidate for reirradiation), clinicians may discuss offering systemic therapy as an alternative, using a regimen with some evidence of activity in the setting of central nervous system (CNS) disease. Evidence quality: low.

Note that examples of circumstances in which a patient would not be a candidate for reirradiation include when the patient has already received WBRT and there is a desire not to retreat with WBRT, when a patient's disease has progressed within a lesion previously treated with SRS, and when a patient's disease has had short or no control with a prior radiotherapy-based approach. There are no randomized phase III trials evaluating systemic approaches in patients with progressive CNS metastases in breast cancer. Selected examples of regimens with CNS activity include capecitabine (based on case series/phase I data), lapatinib plus capecitabine (based on several phase II trials), anthracyclines (based on case series), and platinum agents (based on phase II trials). Clinical trial enrollment should be considered when an appropriate trial is available.

#### Clinical Question D

Should patients with HER2-positive breast cancer be screened for development of brain metastases?

#### *Recommendation VII (screening)*

VIIA. If a patient does not have a known history or symptoms of brain metastases, clinicians should not perform routine surveillance with brain magnetic resonance imaging. Evidence quality: low.

VIIB. Clinicians should have a low threshold for performing diagnostic brain magnetic resonance imaging testing in the setting of any neurologic symptoms suggestive of brain involvement, such as new-onset headaches, unexplained nausea/vomiting, or change in motor/sensory function. Evidence quality: low. Recommendation strength: strong.

Note that this recommendation reflects the high prevalence of brain metastases in patients with HER2-positive metastatic breast cancer and longer survival, as described in the Background section. Suggestive symptoms may include new headaches, vertigo, nausea/vomiting, and/or gait disturbance.

#### Definitions:

#### Guide for Rating Strength of Evidence

Rating for Strength of Evidence	Definition
High	High confidence that the available evidence reflects the true magnitude and direction of the net effect (i.e., balance of benefits v harms) and that further research is very unlikely to change either the magnitude or direction of this net effect.
Intermediate	Moderate confidence that the available evidence reflects the true magnitude and direction of the net effect. Further research is unlikely to alter the direction of the net effect; however, it might alter the magnitude of the net effect.
Low	Low confidence that the available evidence reflects the true magnitude and direction of the net effect. Further research may change either the magnitude and/or direction this net effect.
Insufficient	Evidence is insufficient to discern the true magnitude and direction of the net effect. Further research may better inform the topic. The use of the consensus opinion of experts is reasonable to inform outcomes related to the topic.

#### Guide for Types of Recommendations

Type of Recommendation	Definition
Evidence based	There was sufficient evidence from published studies to inform a recommendation to guide clinical practice.
Formal consensus	The available evidence was deemed insufficient to inform a recommendation to guide clinical practice. Therefore, the Expert Panel used a formal consensus process to reach this recommendation, which is considered the best current guidance for practice. The Panel may choose to provide a rating for the strength of the recommendation (i.e., "strong," "moderate," or "weak"). The results of the formal consensus process are summarized in the guideline and reported in the Data Supplement (see the "Availability of Companion Documents" field).
Informal consensus	The available evidence was deemed insufficient to inform a recommendation to guide clinical practice. The recommendation is considered the best current guidance for practice, based on informal consensus of the Expert Panel. The Panel agreed that a formal consensus process was not necessary for reasons described in the literature review and discussion. The Panel may choose to provide a rating for the strength of the recommendation (i.e., "strong," "moderate," or "weak").
No recommendation	There is insufficient evidence, confidence, or agreement to provide a recommendation to guide clinical practice at this time. The Panel deemed the available evidence as insufficient and concluded it was unlikely that a formal consensus process would achieve the level of agreement needed for a recommendation.

#### Guide for Strength of Recommendations

Rating for Strength of Recommendation	Definition
Strong	There is high confidence that the recommendation reflects best practice. This is based on (1) strong evidence for a true net

Rating for Strength of Recommendation	Definition: (1) strong recommendation, with high confidence that the benefits exceed harms; (2) consistent results, with no or minor exceptions; (3) minor or no concerns about study quality; and/or (4) the extent of panelists' agreement. Other compelling considerations (discussed in the guideline's literature review and analyses) may also warrant a strong recommendation.
Moderate	There is moderate confidence that the recommendation reflects best practice. This is based on (1) good evidence for a true net effect (e.g., benefits exceed harms); (2) consistent results, with minor and/or few exceptions; (3) minor and/or few concerns about study quality; and/or (4) the extent of panelists' agreement. Other compelling considerations (discussed in the guideline's literature review and analyses) may also warrant a moderate recommendation.
Weak	There is some confidence that the recommendation offers the best current guidance for practice. This is based on (1) limited evidence for a true net effect (e.g., benefits exceed harms); (2) consistent results, but with important exceptions; (3) concerns about study quality; and/or (4) the extent of panelists' agreement. Other considerations (discussed in the guideline's literature review and analyses) may also warrant a weak recommendation.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Advanced human epidermal growth factor receptor 2 (HER2)-positive breast cancer and brain metastases

Guideline Category

Management

Treatment

Clinical Specialty

Neurological Surgery

Oncology

Radiation Oncology

Intended Users

Advanced Practice Nurses

Allied Health Personnel

Nurses

Patients

Physician Assistants

Physicians

Guideline Objective(s)

To provide formal expert consensus–based recommendations to practicing oncologists and others on the management of brain metastases for patients with human epidermal growth factor receptor 2 (HER2)–positive advanced breast cancer

## Target Population

Individuals with advanced human epidermal growth factor receptor 2 (HER2)–positive breast cancer and brain metastases

## Interventions and Practices Considered

1. Surgical resection with postoperative radiation
2. Stereotactic radiosurgery (SRS)
3. Whole-brain radiotherapy (WBRT)
4. Fractionated stereotactic radiotherapy (FSRT)
5. Trial of systemic therapy
6. Enrollment in clinical trial
7. Human epidermal growth factor receptor (HER2)-targeted therapy
8. Supportive and palliative care
9. Post-treatment monitoring (serial imaging every 2 to 4 months)
10. Brain magnetic resonance imaging (MRI)

## Major Outcomes Considered

- Overall response rates
- Adverse events
- Progression-free survival (PFS)
- Quality of life (QOL)

## Methodology

### Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

### Description of Methods Used to Collect/Select the Evidence

Systematic Literature Review

American Society for Clinical Oncology (ASCO) guidelines are based on systematic reviews of the literature. A protocol for each systematic review defines parameters for a targeted literature search. Additional parameters include relevant study designs, literature sources, types of reports, and pre-specified inclusion and exclusion criteria for literature identified. The protocol for this guideline was reviewed and approved by the Clinical Practice Guideline Committee's (CPGC's) Methodology Subcommittee and Breast Cancer Guideline Advisory Group (GAG).

Literature Search Strategy

A PubMed search was conducted for studies on patients with human epidermal growth factor receptor 2 (HER2)-positive breast cancer and brain metastases through May 2013. Articles were considered for inclusion in the systematic review of the evidence if they were:

- Fully published or recent meeting presentations of English language reports of phase III randomized clinical trials or rigorously conducted systematic reviews or meta-analyses
- Populated by patients with HER2-positive advanced breast cancer and brain metastases
- Meeting abstracts for which a presentation or poster was available

- Comparative treatment trials

Articles were excluded from consideration in the systematic review if they were (1) meeting abstracts not subsequently published in peer-reviewed journals; (2) editorials, commentaries, letters, news articles, case reports, narrative reviews; (3) published in a non-English language.

Further details on the search strategy and results are provided in Data Supplements 2 and 3 (see the "Availability of Companion Documents" field).

## Number of Source Documents

Fifty-three papers were excluded. Zero papers were reviewed in full text.

## Methods Used to Assess the Quality and Strength of the Evidence

Expert Consensus (Delphi Method)

Weighting According to a Rating Scheme (Scheme Given)

## Rating Scheme for the Strength of the Evidence

Guide for Rating Strength of Evidence

Rating for Strength of Evidence	Definition
High	High confidence that the available evidence reflects the true magnitude and direction of the net effect (i.e., balance of benefits v harms) and that further research is very unlikely to change either the magnitude or direction of this net effect.
Intermediate	Moderate confidence that the available evidence reflects the true magnitude and direction of the net effect. Further research is unlikely to alter the direction of the net effect; however, it might alter the magnitude of the net effect.
Low	Low confidence that the available evidence reflects the true magnitude and direction of the net effect. Further research may change either the magnitude and/or direction this net effect.
Insufficient	Evidence is insufficient to discern the true magnitude and direction of the net effect. Further research may better inform the topic. The use of the consensus opinion of experts is reasonable to inform outcomes related to the topic.

## Methods Used to Analyze the Evidence

Systematic Review

## Description of the Methods Used to Analyze the Evidence

Data Extraction

Data extraction was not conducted, as no literature met the inclusion criteria for the systematic review.

## Methods Used to Formulate the Recommendations

Expert Consensus (Delphi)

## Description of Methods Used to Formulate the Recommendations

None of the data found, including observational studies, were sufficient for making evidence-based recommendations. At that point, the American Society of Clinical Oncology (ASCO) switched to its formal Expert Consensus process (Modified Delphi) for these recommendations.

Guideline Development Process

ASCO convened an Expert Panel on the treatment of patients with advanced human epidermal growth factor 2 (HER2)-positive breast cancer (see Appendix Table A1 in the original guideline document). A brain metastases writing group (subgroup of Expert Panel) met on several occasions and corresponded frequently through e-mail. The Expert Panel members were asked to contribute to the development of the guideline, provide critical review, and finalize the guideline recommendations. The Expert Panel was supplemented by additional experts recruited to rate their agreement with the drafted recommendations as part of the consensus process. The entire membership of experts is referred to as the Consensus Panel (Data Supplement 7 provides a list of members [see "Availability of Companion Documents" field]). All members of the Expert Panel reviewed the draft guideline document, which was then disseminated for external review and submitted to the *Journal of Clinical Oncology* (JCO) for peer review and publication. All ASCO guidelines are ultimately reviewed and approved by the ASCO Clinical Practice Guideline Committee (CPGC) before publication.

The recommendations were developed by a multidisciplinary group of experts using evidence from observational studies and clinical experience as a guide. A literature search for evidence on brain metastases was conducted, but no publications met the inclusion criteria (see the Data Supplement). Therefore, the recommendations were developed by a multidisciplinary group of experts and reviewed by radiation oncologists, neurosurgeons, members of the ASCO Breast Cancer Guidelines Advisory Group, and others using a formal consensus process based on the best available evidence and clinical experience.

The guideline recommendations were crafted, in part, using the Guidelines Into Decision Support (GLIDES) methodology and accompanying BRIDGE- Wiz software (<http://gem.med.yale.edu/BRIDGE-Wiz> ). Ratings for the type of recommendation and strength of the evidence are provided with each recommendation (see the Methodology Supplement [see the "Availability of Companion Documents" field]).

Detailed information about the methods used to develop this guideline is available in the Methodology Supplement, including an overview (panel composition, guideline development process, and revision dates) and descriptions of the formal consensus process and of GLIDES/BRIDGE-Wiz.

Rating Scheme for the Strength of the Recommendations

Guide for Types of Recommendations

Type of Recommendation	Definition
Evidence based	There was sufficient evidence from published studies to inform a recommendation to guide clinical practice.
Formal consensus	The available evidence was deemed insufficient to inform a recommendation to guide clinical practice. Therefore, the Expert Panel used a formal consensus process to reach this recommendation, which is considered the best current guidance for practice. The Panel may choose to provide a rating for the strength of the recommendation (i.e., "strong," "moderate," or "weak"). The results of the formal consensus process are summarized in the guideline and reported in the Data Supplement (see the "Availability of Companion Documents" field").
Informal consensus	The available evidence was deemed insufficient to inform a recommendation to guide clinical practice. The recommendation is considered the best current guidance for practice, based on informal consensus of the Expert Panel. The Panel agreed that a formal consensus process was not necessary for reasons described in the literature review and discussion. The Panel may choose to provide a rating for the strength of the recommendation (i.e., "strong," "moderate," or "weak").
No recommendation	There is insufficient evidence, confidence, or agreement to provide a recommendation to guide clinical practice at this time. The Panel deemed the available evidence as insufficient and concluded it was unlikely that a formal consensus process would achieve the level of agreement needed for a recommendation.

Guide for Strength of Recommendations



Rating for Strength of Recommendation	Definition
Strong	There is high confidence that the recommendation reflects best practice. This is based on (1) strong evidence for a true net effect (e.g., benefits exceed harms); (2) consistent results, with no or minor exceptions; (3) minor or no concerns about study quality; and/or (4) the extent of panelists' agreement. Other compelling considerations (discussed in the guideline's literature review and analyses) may also warrant a strong recommendation.
Moderate	There is moderate confidence that the recommendation reflects best practice. This is based on (1) good evidence for a true net effect (e.g., benefits exceed harms); (2) consistent results, with minor and/or few exceptions; (3) minor and/or few concerns about study quality; and/or (4) the extent of panelists' agreement. Other compelling considerations (discussed in the guideline's literature review and analyses) may also warrant a moderate recommendation.
Weak	There is some confidence that the recommendation offers the best current guidance for practice. This is based on (1) limited evidence for a true net effect (e.g., benefits exceed harms); (2) consistent results, but with important exceptions; (3) concerns about study quality; and/or (4) the extent of panelists' agreement. Other considerations (discussed in the guideline's literature review and analyses) may also warrant a weak recommendation.

## Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

## Method of Guideline Validation

External Peer Review

Internal Peer Review

## Description of Method of Guideline Validation

All members of the Expert Panel reviewed the draft guideline document, which was then disseminated for external review and submitted to *Journal of Clinical Oncology (JCO)* for peer review and publication. All American Society of Clinical Oncology (ASCO) guidelines are ultimately reviewed and approved by the ASCO Clinical Practice Guideline Committee before publication.

The Clinical Practice Guideline Committee approved this guideline update on November 19, 2013.

## Evidence Supporting the Recommendations

### Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

## Benefits/Harms of Implementing the Guideline Recommendations

### Potential Benefits

Appropriate disease management for patients with advanced human epidermal growth factor receptor 2 (HER2)-positive breast cancer and brain metastases

## Potential Harms

- Although whole brain radiotherapy (WBRT) is effective in palliating symptomatic brain metastases, it can be associated with significant acute fatigue, which may persist for 3 to 6 months after WBRT and is thought to reflect white matter demyelination injury. Of particular concern are the neurocognitive sequelae of WBRT. Late effects of WBRT occurring months to years after treatment may include leukoencephalopathy and vascular injury, resulting in increased risk of stroke.
- In one trial, the combination of lapatinib and capecitabine was associated with a 49% grade 3 to 4 toxicity rate, greater than that seen in the short term with radiation therapy approaches such as WBRT or stereotactic radiosurgery (SRS).

## Qualifying Statements

### Qualifying Statements

- The clinical practice guideline and other guidance published herein are provided by the American Society of Clinical Oncology (ASCO) to assist providers in clinical decision making. The information herein should not be relied on as being complete or accurate, nor should it be considered as inclusive of all proper treatments or methods of care or as a statement of the standard of care. With the rapid development of scientific knowledge, new evidence may emerge between the time information is developed and when it is published or read. The information is not continually updated and may not reflect the most recent evidence. The information addresses only the topics specifically identified herein and is not applicable to other interventions, diseases, or stages of diseases. This information does not mandate any particular course of medical care. Furthermore, the information is not intended to substitute for the independent professional judgment of the treating provider, because the information does not account for individual variation among patients. Each recommendation reflects high, moderate, or low confidence that the recommendation reflects the net effect of a given course of action. The use of words like *must*, *must not*, *should*, and *should not* indicates that a course of action is recommended or not recommended for either most or many patients, but there is latitude for the treating physician to select other courses of action in individual cases. In all cases, the selected course of action should be considered by the treating provider in the context of treating the individual patient. Use of the information is voluntary. ASCO provides this information on an as-is basis and makes no warranty, express or implied, regarding the information. ASCO specifically disclaims any warranties of merchantability or fitness for a particular use or purpose. ASCO assumes no responsibility for any injury or damage to persons or property arising out of or related to any use of this information or for any errors or omissions.
- Because many patients for whom guideline recommendations apply present with multiple chronic conditions (MCCs), any management plan needs to take into account the complexity and uncertainty created by the presence of MCCs and highlight the importance of shared decision making around guideline use and implementation. Therefore, in consideration of recommended care for the target index condition, clinicians should review all other chronic conditions present in the patient and take those conditions into account when formulating treatment and follow-up plans (common chronic conditions for patients with breast cancer are listed in the Data Supplement [see the "Availability of Companion Documents" field]). Taking these considerations into account, practice guidelines should provide information on how to apply the recommendations for patients with MCCs, perhaps as a qualifying statement for recommended care. This may mean that some or all of the recommended care options are modified or not applied, as determined by best practice in consideration of any MCC.

## Implementation of the Guideline

### Description of Implementation Strategy

American Society for Clinical Oncology (ASCO) guidelines are developed to be implemented in a variety of health settings. Barriers to implementation and application of the guideline recommendations include factors such as the need to increase awareness among front-line practitioners and cancer survivors and also the need to provide adequate services in the face of limited resources.

This guideline does not consider cost-effectiveness analyses. The guideline Bottom Line was designed to facilitate implementation of recommendations. This guideline will also be distributed through the ASCO Practice Guideline Implementation Network and other ASCO communications. ASCO guidelines are posted on the ASCO Web site and most often published in the *Journal of Clinical Oncology (JCO)*.

For information on the ASCO implementation strategy, please see the [ASCO Web site](#) .

## Implementation Tools

Patient Resources

Quick Reference Guides/Physician Guides

Slide Presentation

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

## Institute of Medicine (IOM) National Healthcare Quality Report Categories

### IOM Care Need

Getting Better

Living with Illness

### IOM Domain

Effectiveness

Patient-centeredness

## Identifying Information and Availability

### Bibliographic Source(s)

Ramakrishna N, Temin S, Chandarlapaty S, Crews JR, Davidson NE, Esteva FJ, Giordano SH, Gonzalez-Angulo AM, Kirshner JJ, Krop I, Levinson J, Modi S, Patt DA, Perez EA, Perlmutter J, Winer EP, Lin NU. Recommendations on disease management for patients with advanced human epidermal growth factor receptor 2-positive breast cancer and brain metastases: American Society of Clinical Oncology clinical practice guideline. *J Clin Oncol*. 2014 Jul 1;32(19):2100-8. [56 references] [PubMed](#)

### Adaptation

Not applicable: The guideline was not adapted from another source.

### Date Released

2014 July 1

### Guideline Developer(s)

American Society of Clinical Oncology - Medical Specialty Society

### Source(s) of Funding

## Guideline Committee

Systemic Therapy for Patients With Advanced Human Epidermal Growth Factor Receptor 2 (HER2)-Positive Breast Cancer Expert Panel

## Composition of Group That Authored the Guideline

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## Financial Disclosures/Conflicts of Interest

### Guideline and Conflicts of Interest

The Expert Panel was assembled in accordance with the American Society of Clinical Oncology (ASCO) Conflicts of Interest Management Procedures for Clinical Practice Guidelines (summarized at <http://www.asco.org/rwc> ). Members of the panel completed the ASCO disclosure form, which requires disclosure of financial and other interests that are relevant to the subject matter of the guideline, including relationships with commercial entities that are reasonably likely to experience direct regulatory or commercial impact as a result of promulgation of the guideline. Categories for disclosure include employment relationships, consulting arrangements, stock ownership, honoraria, research funding, and expert testimony. In accordance with these procedures, the majority of the members of the panel did not disclose any such relationships.

### Authors' Disclosures of Potential Conflicts of Interest

*Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about American Society of Clinical Oncology's (ASCO's) conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.* Employment or Leadership Position: None Consultant or Advisory Role: Francisco J. Esteva, Genentech (C), Novartis (C); Ana M. Gonzalez-Angulo, Genentech (C), Novartis (C); Ian Krop, Genentech (U), Roche (U); Eric P. Winer, AstraZeneca (U), Genentech (U), Novartis (U), Pfizer (U); Nancy U. Lin, Genentech (U), GlaxoSmithKline (C), Novartis (C) Stock Ownership: None Honoraria: Naren Ramakrishna, Brainlab Ag Research Funding: Sarat Chandarlapaty, Puma; Ana M. Gonzalez-Angulo, Bristol-Myers Squibb, Genentech, GlaxoSmithKline, Novartis; Ian Krop, Genentech, Roche; Shanu Modi, Genentech, Novartis, Synta Pharmaceuticals; Edith A. Perez, Genentech, GlaxoSmithKline; Eric P. Winer, Genentech; Nancy U. Lin, Genentech, GlaxoSmithKline, Novartis, Array Biopharma, Geron Expert Testimony: None Patents, Royalties, and Licenses: None Other Remuneration: Eric P. Winer, Genentech

## Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

## Guideline Availability

Electronic copies: Available from the [American Society of Clinical Oncology \(ASCO\) Web site](#) .

Print copies: Available from American Society of Clinical Oncology, Cancer Policy and Clinical Affairs, 2318 Mill Rd, Suite 800, Alexandria, VA 22314; E-mail: [guidelines@asco.org](mailto:guidelines@asco.org)

## Availability of Companion Documents

The following are available:

- Recommendations on disease management for patients with advanced human epidermal growth factor receptor 2-positive breast cancer and brain metastases: American Society of Clinical Oncology clinical practice guideline. Data supplement. Alexandria (VA): American Society of Clinical Oncology; 2014. 16 p. Electronic copies: Available from the [American Society of Clinical Oncology \(ASCO\) Web site](#) .
- Recommendations on disease management for patients with advanced HER2-positive breast cancer and brain metastases: American Society of Clinical Oncology clinical practice guideline. Methodology supplement. Alexandria (VA): American Society of Clinical Oncology; 2014. 9 p. Electronic copies: Available from the [ASCO Web site](#) .
- Recommendations on disease management for patients with advanced HER2-positive breast cancer and brain metastases: American Society of Clinical Oncology clinical practice guideline. Slide set. Alexandria (VA): American Society of Clinical Oncology; 2014. 24 p. Electronic copies: Available in [PDF](#)  and [PowerPoint](#)  from the ASCO Web site.
- Recommendations on disease management for patients with advanced human epidermal growth factor receptor 2-positive breast cancer and brain metastases: American Society of Clinical Oncology clinical practice guideline. Summary of recommendations: Table 2. Alexandria (VA): American Society of Clinical Oncology; 2014. 10 p. Electronic copies: Available from the [ASCO Web site](#) .

## Patient Resources

The following is available:

- Treatment of metastatic HER2-positive breast cancer. American Society of Clinical Oncology (ASCO) care and treatment recommendations for patients. 2014 May 5. Electronic copies: Available from the [Cancer.Net Web site](#) .

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

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